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## NOACs in Anesthesiology

Spahn, Donat R ; Beer, Jürg-Hans ; Borgeat, Alain ; Chassot, Pierre-Guy ; Kern, Christian ; Mach, François ; Nedeltchev, Krassen ; Korte, Wolfgang

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# NOACs in Anesthesiology

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## Keywords

New oral anticoagulants · Direct oral anticoagulants · Anesthesiology · Xa antagonist · Thrombin inhibitor

## Summary

**Background:** Due to increasing use of new oral anticoagulants (NOACs), clinicians are faced more and more frequently with clinical issues related to these drugs. **Objective:** The objective of this publication is to make practical suggestions for the perioperative management of NOACs as well as for their handling in overdoses and bleedings. **Recommendations:** In elective surgery and creatinine clearance  $\geq 50$  ml/min, a NOAC should be discontinued 24–36 h before the intervention, and even earlier in case of reduced kidney function. In emergency interventions that cannot be delayed, the management is dependent on the NOAC plasma levels. With levels  $\leq 30$  ng/ml, surgery can be performed. With levels  $>30$  ng/ml, reversal agents should be considered. In low bleeding risk surgery, NOACs can be re-started 24 h after the intervention, which is prolonged to 48–72 h after surgery with high bleeding risk. In case of NOAC overdose and minor bleedings, temporary discontinuation and supportive care are usually sufficient to control the situation. In severe or life-threatening bleedings, nonspecific and specific reversal agents should be considered.

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## Introduction

New oral anticoagulant (NOAC) agents have been increasingly used in the prevention and treatment of thromboembolic events in the last few years. The four NOACs currently available in Europe directly target and inhibit either factor Xa (apixaban, edoxaban and rivaroxaban) or thrombin (dabigatran).

In addition to having numerous practical advantages – simple dosage schemes and no need for laboratory monitoring – over previous treatments using vitamin K antagonists (VKAs), NOACs are also demonstrating clinical benefits. Meta-analyses and systematic reviews comparing NOACs to the VKA warfarin provided evidence of NOACs having similar to superior efficacy in preventing stroke and systemic thromboembolic events in patients with non-valvular atrial fibrillation (nvAF), while significantly reducing the likelihood of major and especially intracranial bleeding [1–5].

While all four available NOACs are indicated and have proven efficacy in patients with nvAF as well as for treatment and secondary prophylaxis of deep-vein thrombosis and pulmonary embolism [6–12], only three (dabigatran, apixaban, rivaroxaban) have so far been cleared for the prevention of thromboembolic events after major knee or hip surgery in Europe and the US [13–18]. Only two (apixaban, rivaroxaban) are currently available for this indication in Switzerland [6, 7, 19] (table 1).

**Table 1.** Approved indications and dosages of NOACs

	Dabigatran, mg/day	Apixaban, mg/day	Edoxaban, mg/day	Rivaroxaban, mg/day
<i>Switzerland (swissmedicinfo.ch)</i>				
nvAF	2 × 150 2 × 110 <sup>1</sup>	2 × 5 2 × 2.5 <sup>3</sup>	1 × 60 1 × 30 <sup>6</sup>	1 × 20 1 × 15 <sup>7,8</sup>
Therapy DVT/PE	2 × 150 <sup>2</sup>	2 × 10 for 7 days, then 2 × 5	1 × 60 <sup>2</sup> 1 × 30 <sup>6</sup>	2 × 15 for 3 weeks, then 1 × 20
Prevention of recurrent DVT/PE	2 × 150 2 × 110 <sup>1</sup>	2 × 2.5	1 × 60	1 × 20
Prevention of TE in major hip or knee surgery	–	2 × 2.5 <sup>4,5</sup>	–	1 × 10 <sup>9,10</sup>
<i>Europe (EMA)<sup>16</sup></i>				
nvAF	2 × 150 2 × 110 <sup>11</sup>	2 × 5 2 × 2.5 <sup>13</sup>	1 × 60 1 × 30 <sup>17</sup>	1 × 20 1 × 15 <sup>7,8</sup>
Therapy DVT/PE	2 × 150 2 × 110 <sup>11</sup>	2 × 10 for 7 days, then 2 × 5	1 × 60 1 × 30 <sup>17</sup>	2 × 15 for 3 weeks, then 1 × 20
Prevention of recurrent DVT/PE	2 × 150 2 × 110 <sup>11</sup>	2 × 5 2 × 2.5 <sup>14</sup>	1 × 60 1 × 30 <sup>17</sup>	1 × 20 1 × 10 <sup>14,18</sup>
Prevention of TE in major hip or knee surgery	1 × 110 mg first day, then 2 × 110 <sup>12</sup>	2 × 2.5 <sup>15</sup>	–	1 × 10 <sup>10</sup>
Prevention of atherothrombotic events after ACS with elevated cardiac biomarkers	–	–	–	2 × 2.5 <sup>9,19</sup>
Prevention of atherothrombotic events in CAD or symptomatic PAD	–	–	–	2 × 2.5 <sup>9,20</sup>

Table 1 continued on next page

Rivaroxaban, in combination with low-dose acetylsalicylic acid (ASA), is approved in Europe and the US for prevention of major cardiovascular events in patients with chronic coronary artery disease (CAD) or peripheral arterial disease (PAD) [13, 16].

Due to the widespread use of NOACs, clinicians are faced more and more frequently with issues concerning the perioperative management of such patients.

The aim of this publication is to provide a practical update about NOACs for the perioperative setting. It contains an overview of the pharmacological characteristics of the available NOACs and suggestions for procedures for the respective perioperative management of elective and emergency interventions. Other clinical situations, such as overdoses and bleeding under NOACs, will be addressed as well.

### Key Factors for the Preoperative Estimation of Bleeding Risk in NOAC Patients

The intra- and postoperative bleeding risk is influenced by the product and application characteristics of the NOAC, patient-related factors, and the type of intervention. High bleeding risk means that a patient is at risk of losing a large amount of blood or bleeding occurs in a critical, closed space with potentially severe consequences.

### NOACs: Approved Indications and Dosages

All NOACs block an activated coagulation factor, either FXa (apixaban, edoxaban, rivaroxaban) or FIIa (thrombin; dabigatran), thus halting the coagulation cascade and preventing clot formation. Despite the similar mode of action, the different NOACs vary in several practically relevant aspects, such as their approved indications, pharmacokinetic properties, and dosage schemes. In table 1 the approved indications and corresponding dosage schemes recommended by Swiss, European and US American drug information agencies are listed. However, for some patients an adaptation of the dosage is advised, as age, body weight, and renal or liver functions can have an influence on the drug's dynamics [6–9, 20].

### Pharmacokinetic Profiles

In order to perform surgery at a time of minimal bleeding risk, the timing of last intake and the pharmacokinetic properties of the NOAC used have to be considered, some of which are summarized in table 2. Especially the time to peak concentration ( $T_{\max}/C_{\max}$ ), the half-life ( $T_{1/2}$ ) and the elimination pathway are important pieces of information that should be factored in patient management.

### Drug Interactions

NOACs were developed to offer advantageous treatment alternatives to the VKAs [24, 25]. The reduction of

**Table 1.** Continued

	Dabigatran, mg/day	Apixaban, mg/day	Edoxaban, mg/day	Rivaroxaban, mg/day
USA (FDA)				
nvAF	2 × 150 <sup>21</sup> 2 × 75 <sup>22,23</sup>	2 × 5 2 × 2.5 <sup>25</sup>	1 × 60 <sup>27</sup> 1 × 30 <sup>28</sup>	1 × 20 <sup>29</sup> 1 × 15 <sup>30</sup>
Therapy DVT/PE	2 × 150 <sup>21</sup>	2 × 10 for 7 days, then 2 × 5	1 × 60 1 × 30 <sup>28</sup>	2 × 15 for 3 weeks, then 1 × 20
Prevention of recurrent DVT/PE	2 × 150 <sup>21</sup>	2 × 5 2 × 2.5 <sup>14</sup>	no mention	1 × 20 1 × 10 <sup>14,18</sup>
Prevention of TE in major hip or knee surgery	1 × 110 mg first day, then 1 × 220 <sup>24</sup>	2 × 2.5 <sup>26</sup>	–	1 × 10 <sup>26</sup>
Risk reduction of major CV events (CV death, MI, and stroke) in chronic CAD or PAD	–	–	–	2 × 2.5 <sup>9,20</sup>

nvAF = Non-valvular atrial fibrillation; DVT = deep-vein thrombosis; PE = pulmonary embolism; TE = thromboembolism; EMA = European Medicines Agency; ACS = acute coronary syndrome; CAD = coronary artery disease; PAD = peripheral arterial disease; FDA = Food and Drug Administration; CV = cardiovascular.

<sup>1</sup>CrCl 30–50 ml/min, or >80 years.

<sup>2</sup>After initial treatment with UFH or LMWH for 5 days.

<sup>3</sup>Patients with at least two of the following criteria: age ≥ 80 years, body weight ≤ 60 kg, or serum creatinine ≥ 1.5 mg/dl (133 μmol/l).

<sup>4</sup>Duration of treatment: hip replacement 32–38 days, knee replacement 10–14 days.

<sup>5</sup>Indication: elective hip and knee replacement.

<sup>6</sup>CrCl 15–50 ml/min, body weight ≤ 60 kg, or concomitant therapy with potent P-gp inhibitors.

<sup>7</sup>CrCl 30–49 ml/min.

<sup>8</sup>Rivaroxaban is also admitted for CrCl 15–29 ml/min; careful application required, no dosage recommendation.

<sup>9</sup>Can be taken independent of food, whereas 15 mg and 20 mg should be taken with food to assure bioavailability.

<sup>10</sup>Duration of treatment: major hip surgery 5 weeks, major knee surgery 2 weeks.

<sup>11</sup>Age ≥ 80 years, or patients receiving concomitant verapamil.

<sup>12</sup>Duration of treatment: hip replacement 28–35 days, knee replacement 10 days.

<sup>13</sup>Patients with at least two of the following criteria: age ≥ 80 years, body weight ≤ 60 kg, or serum creatinine ≥ 1.5 mg/dl (133 μmol/l).

<sup>14</sup>After at least 6 months of treatment for DVT or PE.

<sup>15</sup>Duration of treatment: hip replacement 32–38 days, knee replacement 10–14 days.

<sup>16</sup>EMA advises that ‘edoxaban should only be used in patients with nvAF and high creatinine clearance after careful evaluation of the individual thromboembolic and bleeding risk’.

<sup>17</sup>Patients with one or more of the following clinical factors: CrCl 15–50 ml/min, body weight ≤ 60 kg, concomitant use of P-gp inhibitors.

<sup>18</sup>Patients with high risk of recurrent DVT/PE consider administering 1 × 20 mg/day.

<sup>19</sup>In combination with acetylsalicylic acid (1 × 75–100 mg/day) or acetylsalicylic acid (1 × 75–100 mg/day) in addition to either clopidogrel (1 × 75 mg/day) or a standard dose of ticlopidine (once daily).

<sup>20</sup>In combination with acetylsalicylic acid (1 × 75–100 mg/day).

<sup>21</sup>CrCl > 30 ml/min.

<sup>22</sup>CrCl between 15 and 30 ml/min.

<sup>23</sup>If given with P-gp inhibitors dronedarone or systemic ketoconazole.

<sup>24</sup>Duration of treatment: hip replacement 28–35 days.

<sup>25</sup>Patients with at least two of the following criteria: age ≥ 80 years, body weight ≤ 60 kg, or serum creatinine ≥ 1.5 mg/dl.

<sup>26</sup>Duration of treatment: hip replacement 35 days, knee replacement 12 days.

<sup>27</sup>FDA provides a boxed warning that ‘edoxaban should not be used in patients with CrCl > 95 ml/min.

<sup>28</sup>For patients with CrCl 15–50 ml/min.

<sup>29</sup>If CrCl > 50 ml/min.

<sup>30</sup>If CrCl 15–50 ml/min.

drug/drug and drug/food interactions are among the most relevant advantages of NOACs over VKAs [24, 26]. As NOACs are partially eliminated through P-glycoproteins (P-gp) transport proteins and cytochrome P450 enzymes, there is still a potential of interference with drugs that use the same pathways. Such interactions may ultimately lead to over- or under-anticoagulation [27].

Recommendations are mainly based on pharmacokinetic studies measuring plasma levels of drugs with the same metabolic pathways as NOACs, as only little data is

available on the bleeding risk of combining NOACs with other medications. A new population-based cohort study with over 90,000 atrial fibrillation (AF) patients found a high risk of major bleeding for NOAC patients who were also taking amiodarone and fluconazole, in line with their respective pharmacokinetic data. Surprisingly, the higher risk of major bleeding was also prevalent for NOAC patients taking rifampicin and phenytoin, which, according to their pharmacokinetic profiles, lead to lower NOAC plasma levels – an unexplained fact caused by an un-

**Table 2.** Pharmacokinetic characteristics of NOACs [6–9, 21]

	Dabigatran	Apixaban	Edoxaban	Rivaroxaban
Bioavailability	6.5%	52% <sup>1</sup>	62%	80–100% (10 mg) 66–100% (20 mg)
Prodrug	yes	no	no	no
T <sub>max</sub>	0.5–2 h	3–4 h	1–2 h	2–4 h
T <sub>1/2</sub>	12–14 h	12 h (18–40y) 15 h (>65y)	10–14 h	5–9 h 11–13 h (elderly patients)
Trough median (P10–P90), or anti-FXa minimum median [21]	2 × 110 mg/day: 66 (28–155) ng/ml 2 × 150 mg/day: 93 (40–215) ng/ml	2 × 2.5 mg/day: 0.84 (0.37–1.8) IU/ml 2 × 5 mg/day: 1.54 (0.61–3.43) IU/ml	1 × 30 mg/day: 0.35 (0.21–0.57) IU/ml 1 × 60 mg/day: 0.64 (0.37–1.12) IU/ml	2 × 15 mg/day: 57 (20–140) ng/ml 1 × 20 mg/day: 25.6 (5.93–86.9) ng/ml
Peak median (P10–P90), or anti-FXa maximum median [21]	2 × 110 mg/day: 133 (52–275) ng/ml 2 × 150 mg/day: 184 (74–383) ng/ml	2 × 2.5 mg/day: 1.3 (0.67–2.4) IU/ml 2 × 5 mg/day: 2.55 (1.36–4.79) IU/ml	1 × 30 mg/day: 2.1 IU/ml 1 × 60 mg/day: 3.8 IU/ml	2 × 15 mg/day: 229 (180–320) ng/ml 1 × 20 mg/day: 255 (189–419) ng/ml
Elimination [22]	80% renal 20% hepatic	27% renal 73% hepatic	35% renal 65% hepatic	33% renal 33% hepatic 33% unchanged in urine
Distribution volume	60–70 l	21 l	107 l	50 l
Duration of action [23]	24–36 h	24 h		24 h
Interaction [21]	substrate of P-gp	metabolized by CYP3A4 and substrate of P-gp	substrate of P-gp, very little metabolism by CYP450	metabolized by CYP3A4, CYP2J2 and substrate of P-gp and BCRP
Interference with food [21]	prolongs C <sub>max</sub> to 2 h	none	none	increases AUC <sup>2</sup> to 39%

T<sub>max</sub> = Time to maximum plasma concentration; T<sub>1/2</sub> = half-life, time to 50% of maximum plasma concentration; FXa = factor Xa; P-gp = P-glycoprotein; CYP3A4 = cytochrome P450 3A4; CYP450 = cytochrome P450; CYP2J2 = cytochrome P450 2J2; BCRP = breast cancer resistance protein; C<sub>max</sub> = maximum plasma concentration; AUC = area under the curve.

<sup>1</sup>No effect of meals.

<sup>2</sup>AUC = Area under curve (plasma concentration-time curve).

known mechanism. Bleeding rates when taking other drugs that either inhibit CYP 3A4 or compete for P-gp, were not found to be increased [28]. Although this study with a Taiwanese population may not be generalized to Western patients, one should be mindful of amiodarone, especially in the perioperative setting, as it is a frequently used drug amongst NOAC users.

If co-administration of a NOAC with interacting agents cannot be avoided, then a monitoring could be beneficial before a surgical intervention [7, 22]. Details are summarized in table 3.

#### *Disorders and Interventions with Increased Risk of Bleeding*

The bleeding risk of a patient undergoing surgery depends on the type of intervention, the patient's individual characteristics, and the co-medication used. Disorders known to increase a patient's susceptibility to bleeding are shown in table 4.

#### *Bleeding Risk of Surgical Interventions*

Usually emergency surgery is associated with high or increased bleeding risk. Many surgical interventions also increase the thromboembolic risk. So, both risks – the one for bleeding and the one for thromboembolic events – must be balanced [30]. In table 5 bleeding and thromboembolic risks for common surgeries are listed.

#### *Coagulation Tests / Monitoring*

The NOACs' pharmacodynamic and pharmacokinetic profiles are well known, which makes their anticoagulation effects relatively predictable. Therefore, patients using NOACs do not require routine coagulation monitoring [6, 7, 9, 22, 31].

However, in certain clinical circumstances specific coagulation tests are crucial, for example in situations of major bleeding, emergency surgery, stroke during treatment, or when the patient has developed renal failure [32].

NOAC-specific tests have to be used which measure the plasma drug level (µg/ml) or the anti-FXa activity (IU/



**Table 3.** Drug-drug interactions: effect on NOAC plasma-levels, adapted from [29]

Drug	Mechanism	Dabigatran	Apixaban	Edoxaban	Rivaroxaban
<i>Antiarrhythmic drugs</i>					
Amiodarone	moderate P-gp competition	↑ – ↑↑	no data	↑↑	(↑)
Digoxin	P-gp competition	no effect	no effect	no effect	no effect
Diltiazem	P-gp competition and weak CYP3A4 inhibition	no effect	↑↑	no data	(↑)
Dronedarone	P-gp competition and CYP3A4inhibition	↑↑↑ – ↑↑↑↑	no data	↑↑↑	no data
Quinidine	P-gp competition	↑↑	no data	↑↑↑	no data
Verapamil	P-gp competition (and weak CYP3A4 inhibition)	↑ – ↑↑↑↑	no data	↑↑	(↑)
<i>Other cardiovascular drugs</i>					
Atorvastatin	P-gp competition and CYP3A4 inhibition	↑	no data	no effect	no effect
Antibiotics Clarithromycin; erythromycin	moderate P-gp competition and CYP3A4 inhibition	↑	no data	↑↑↑	↑ – ↑↑
Rifampicin	P-gp/ BCRP and CYP3A4/CYP2J2 inducers	↓↓	↓↓	↓↓ compensatory increase of active metabolites	↓↓
<i>Antiviral drugs</i>					
HIV protease inhibitors (e.g. ritonavir)	P-gp and BCRP competition or inducer; CYP3A4 inhibition	no data	↑↑↑↑	no data	↑↑↑↑
<i>Fungostatics</i>					
Fluconazole	moderate CPY3A4 inhibition	no data	no data	no data	↑↑
Itraconazole; ketoconazole; posaconazole; voriconazole	potent P-gp and BCRP competition; CYP3A4 inhibition	↑↑↑↑	↑↑↑↑	↑↑↑ – ↑↑↑↑	↑↑↑↑
<i>Immunosuppressives</i>					
Cyclosporin; tacrolimus	P-gp competition	not recommended	no data	↑↑↑	no data
<i>Antiphlogistics</i>					
Naproxen	P-gp competition	no data	↑↑	no effect	no data
<i>Antacids</i>					
H2B; PPI; Al-Mg-hydroxide	gastrointestinal absorption	↓	no effect	no effect	no effect
<i>Others</i>					
Carbamazepine, phenobarbital, phenytoin	P-gp/BCRP and CYP3A4/CYP2J2 inducers	↓↓↓	↓↓	↓↓	↓↓

P-gp = P-glycoprotein; CYP3A4 =cytochrome P450 3A4; BRCP = breast cancer resistance protein; CYP2J2 = cytochrome P450 2J2; GI ↑ up to 30%, ↑↑ up to 60%, ↑↑↑ up to 90%, ↑↑↑↑ > 90%.

**Table 4.** Anamnestic risk factors and current disorders with increased bleeding risk

<ul style="list-style-type: none"> <li>- Coagulation disorders</li> <li>- Platelet disorders</li> <li>- Active gastrointestinal ulcers</li> <li>- Recent major bleeding (particularly intracranial)</li> <li>- Recent biopsy, surgery or major trauma</li> <li>- Bacterial endocarditis</li> <li>- Liver disease (Child Pugh A, B)</li> <li>- Severe renal failure</li> </ul>
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ml). It is important to note, however, that prospective endpoint-driven studies assessing the effect of monitoring (± dosing adaptations based on these measurements) are lacking; as such, these measurements need to be performed and interpreted by specialists and should not be performed on a routine basis even in difficult/high-risk patients.

Also, in NOAC patients it may be indicated to carry out routine coagulation tests to assess the general coagulation status, especially when bleeding occurred or preoperatively.

**Table 5.** Bleeding risk of elective surgeries, adapted from [30]

	High risk	Medium risk	Low risk
Bleeding complications	intracranial surgery spinal canal surgery  orbital surgery / posterior chamber major tumor surgery  heart surgery thyroid gland surgery  liver and pancreas resection	remaining surgeries colonoscopy, especially for biopsy and polypectomy ERCP with papillotomy  biopsies of parenchymatous organs  bronchoscopy with biopsies serial teeth extractions, operative tooth extraction, oral surgery	transurethral surgery esophago-gastro-duodenoscopy, endosonography skin biopsies  dental hygiene, periodontal surgery, dental treatments (except serial teeth extractions)
Thromboembolic complications	endoprosthesis  proximal hip fractures and plurifragmentary fractures major pelvic surgery  tumor surgery	surgery on upper extremities and all remaining interventions on lower extremities major visceral, urological and gynecological surgeries (>30 min)  lung, chest wall and mediastinum surgeries varicose vein surgery vascular surgery	minor visceral, urological and gynecological surgeries (<30 min) with no bed rest orthopedic removal of metal with no bed rest and no impairment of joint mobility

**Table 6.** Interpretation of coagulation tests under NOAC, adapted from [34]

Test	Effect of dabigatran	apixaban	edoxaban	rivaroxaban
PT/INR	–	(↑)	(↑) <sup>1</sup>	↑
aPTT	↑↑	(↑)	(↑) <sup>1</sup>	(↑)
TT	↑↑↑	–	–	–
Anti-FXa	–	↑↑	↑↑	↑↑

PT = Prothrombin time; INR = internationalized normalized ratio; aPTT = activated prothrombin time; TT = thrombin time; FXa = factor Xa.

↑ Prolonged coagulation test or elevated anti-FXa plasma levels.

<sup>1</sup> Prolonged, but no known relation with bleeding risk [29].

Table 6 may help with the interpretation of the test results, for which it is important to consider the time of last intake of the NOAC and the renal function [33].

Prothrombin time (PT): Even though PT is not the most effective test available, it is still widely used in practice for screening [35]. PT is generally not a recommended test for the direct FXa inhibitors as there is a high variability and normal values do not exclude clinically relevant levels of the drugs [7, 8, 36, 37]. PT seems to be more sensitive towards rivaroxaban than to other FXa inhibitors [6, 33, 38]. PT is not sensitive to dabigatran, thus not recommended for its quantification [9].

Activated partial thromboplastin time (aPTT): Due to widespread use, around the clock availability, low cost

and relatively good sensitivity, aPTT may be used for the monitoring of dabigatran and as a screening test for the risk of bleeding [39]. Again, this test is not useful and not recommended for rivaroxaban, apixaban and edoxaban, as values show a high variability [6–8, 33, 36].

The aPTT could be useful for an urgent assessment of the presence of dabigatran, although normal values might still indicate a presence of the drug [33, 40].

Thrombin time (TT): This test is mainly useful to screen for the presence or absence of dabigatran, it is not useful for the direct FXa inhibitors [6–8, 34, 35]. A normal TT excludes the presence of dabigatran [41].

Anti-FXa: For rivaroxaban, apixaban and edoxaban the most accurate measurement of plasma concentration is done with the anti-FXa assay using the specific drug as calibrator [6–8, 33, 34, 37]. In some clinics these tests are available 24/7 with results obtained in about 20 min, thus being a valid method even in urgent situations [22].

## Perioperative Management of NOACs

### Elective Interventions

The objective of the peri-interventional management of patients already under NOAC before surgery is to minimize the peri-interventional risk for thromboembolism and bleeding.

Except for surgical interventions with very low risk of bleeding, NOAC therapy needs to be interrupted [42, 43]. Bridging is not recommended, as it has not been found to

**Table 7.** Time of last drug intake, adapted from [29, 51]

	Surgery with low risk of bleeding	Surgery with high risk of bleeding
Dabigatran (dose depending on age and renal function) CrCl $\geq 50$ ml/min ( $t_{1/2} = 15$ h) CrCl $\geq 30 - <50$ ml/min ( $t_{1/2} = 18$ h)	24–36 h before surgery 48 h before surgery	48–72 h before surgery 96 h before surgery <sup>1</sup>
Apixaban ( $2 \times 2.5$ mg / $2 \times 5$ mg/day) Normal or mild insufficiency (CrCl $> 50$ ml/min) ( $t_{1/2} = 7-8$ h) Moderate insufficiency (CrCl 30–50 ml/min) ( $t_{1/2} = 17-18$ h)	24 h before surgery 48 h before surgery	48 h before surgery 48 h before surgery
Edoxaban (dose depending on age, body weight, renal function) Normal or mild insufficiency (CrCl $> 50$ ml/min) ( $t_{1/2} = 10-14$ h) Moderate insufficiency (CrCl 30–50 ml/min) ( $t_{1/2} = 10-14$ h)	24 h before surgery 48 h before surgery <sup>2</sup>	48 h before surgery 72 h before surgery <sup>2</sup>
Rivaroxaban ( $1 \times 15$ mg / $1 \times 20$ mg/day) Normal or mild insufficiency (CrCl $> 50$ ml/min) ( $t_{1/2} = 8-9$ h) Moderate insufficiency (CrCl 30–50 ml/min) ( $t_{1/2} = 9$ h) Severe insufficiency (CrCl 15–29.9 ml/min) ( $t_{1/2} = 9$ h)	24 h before surgery <sup>3</sup> 24 h before surgery 48 h before surgery	48 h before surgery 48 h before surgery 72 h before surgery

CrCl = Creatinine clearance;  $t_{1/2}$  = half-life, 50% of maximum plasma concentration.

<sup>1</sup>Dabigatran is eliminated mainly by the kidneys (80%); the delay should be prolonged in case of renal insufficiency.

<sup>2</sup>Edoxaban depends on renal elimination more than rivaroxaban or apixaban. The delay should be increased in case of renal insufficiency.

<sup>3</sup>In patients without comorbidities taking 10 mg/d and scheduled for low bleeding risk surgery, the delay can be shortened to 24 h.

**Table 8.** Timing of NOAC re-start after surgery [51]

Drug	Low bleeding risk surgery	High bleeding risk surgery
Dabigatran	resume 24 h after surgery, $2 \times 150$ mg/day <sup>1</sup>	resume 48-72 h after surgery, $2 \times 150$ mg/day <sup>1,2,6</sup>
Rivaroxaban	resume 24 h after surgery, $1 \times 20$ mg/day <sup>1</sup>	resume 48-72 h after surgery, $1 \times 20$ mg/day <sup>1,3,6</sup>
Apixaban	resume 24 h after surgery, $2 \times 2.5$ mg/day <sup>1</sup>	resume 48-72 h after surgery, $2 \times 2.5$ mg/day <sup>1,4,6</sup>
Edoxaban	resume 24 h after surgery, $1 \times 60$ mg/day <sup>1</sup>	resume 48-72 h after surgery, $1 \times 30$ mg/day <sup>1,5,6</sup>

<sup>1</sup>Or the pre-operative, indicated dosage [51].

<sup>2</sup>For patients at high risk for thromboembolism, consider administration of a reduced dose of dabigatran (e.g.  $1 \times 110-150$  mg/day) on the evening after surgery and on the following day (first postoperative day) after surgery [59].

<sup>3</sup>For patients at high risk for thromboembolism, consider administration of a reduced dose of rivaroxaban (e.g.  $1 \times 10$  mg/day) on the evening after surgery and on the following day (first postoperative day) after surgery [59].

<sup>4</sup>For patients at high risk for thromboembolism, consider administration of a reduced dose of apixaban (e.g.  $2 \times 2.5$  mg/day) on the evening after surgery and on the following day (first postoperative day) after surgery [51].

<sup>5</sup>For patients at high risk for thromboembolism, consider administration of a reduced dose of edoxaban (e.g.  $1 \times 30$  mg/day) on the evening after surgery and on the following day (first postoperative day) after surgery [51].

<sup>6</sup>LMWH such as enoxaparin  $1 \times 40$  or  $2 \times 30$  mg/day or mechanical prophylaxis such as intermittent pneumatic compression can be considered until therapeutic anticoagulation can be re-introduced [59].

reduce thromboembolic events, but does increase the bleeding risk [42, 44–46]. In cases where interruption is not necessary, procedures should be undertaken at trough and not at peak levels of NOAC.

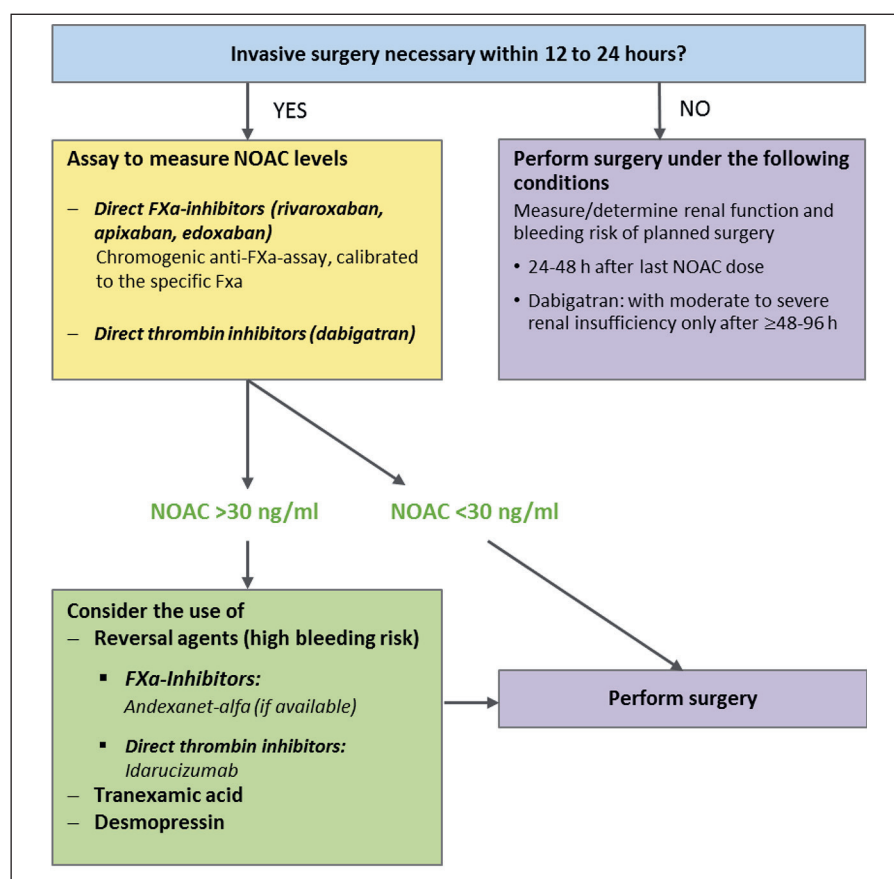
Recommendations about pre-interventional discontinuation of NOACs vary. While for interventions with low bleeding risk an interruption of NOACs of  $\geq 24$  h is often considered as sufficient, the proposed period of time for interventions with high bleeding risk is between 2 and 5 days, for dabigatran up to 7 days [20, 29, 47, 48]. These recommendations are not supported by clinical outcome data, but they rely on pharmacokinetic calculations

using elimination half-lives to predict NOAC levels with minimal bleeding risk.

It is usually assumed that an interruption of two to three half-lives of the drug is safe for low and intermediate hemorrhagic risk, and of four to five half-lives for high bleeding risk and neuraxial anesthesia. Renal insufficiency therefore may prolong these periods, depending on the specific NOAC and its renal elimination.

The recently published CORDIA study examined the necessary discontinuation period to reach NOAC levels of  $\leq 30$  ng/ml, which were assumed to carry minimal bleeding risk [43]. Only 5% had NOAC levels of  $>30$  ng/ml





**Fig. 1.** Emergency intervention schema, adapted after [54].

after 49–2 h, and none >50 ng/ml. These figures were observed in patients with normal and reduced renal function, making it difficult to derive differentiated recommendations. For shorter discontinuation periods, there was a significant interindividual variability of plasma levels [43]. Another publication reported plasma levels of rivaroxaban that were higher than expected in patients with impaired kidney function (glomerular filtration rate < 60 ml/min) and with co-medication amiodarone [49]. In unclear situations, it remains reasonable to measure NOAC plasma levels.

Based on the limited available data, the NOAC-free interval before intervention/surgery for patients with low bleeding risk and normal renal function should be ≥24 h (for details see table 7). Provided there is no clinical evidence of disturbed hemostasis, the NOAC can be re-started the day after the intervention (table 8). In patients with high bleeding risk and normal renal function the NOAC-free interval before intervention/surgery is usually ≥48 h (for details see table 7), and re-start of the NOAC may take place on day 2 or 3 after the intervention, provided there are no signs of disturbed hemostasis or surgical contraindications [31] (table 8).

The PAUSE trial is expected to provide more data on the timing of last intake, plasma levels, and clinical outcome of NOACs [50].

### Emergency Interventions

In emergency situations it is important to know the type of NOAC involved, the time of last intake, and the patient's renal function. If NOAC elimination is normal, the duration of action is 24 h for FXa antagonists and 24–36 h for dabigatran [23] (tables 2 and 7). Therefore, whenever possible, an intervention/surgery should be delayed by 24–48 h after last NOAC intake, in case of renal insufficiency even more (table 7) [51]. It may be helpful to know the NOAC plasma level, especially when the time of last intake is unknown or a relevant plasma level might still be present. The latter may be expected particularly in patients of advanced age (>75/80 years), low body weight (<60 kg), and/or compromised renal function (creatinine clearance < 50 ml/min). If it is unclear whether the test result represents a value from the ascending or descending slope of the NOAC plasma level curve, a second test after 3–4 h may bring clarification [31].

If an operation cannot be delayed, the further approach is based on the NOAC plasma level, provided there are no other obstacles. For the interpretation of the plasma level values, the time of last NOAC intake and renal function are important. Only little data is available on the relation between NOAC plasma levels and the bleeding risk in surgical interventions. Levels < 30 ng/ml are considered safe for high bleeding risk interventions,

**Table 9.** Measures to influence the absorption and elimination of NOACs

	Dabigatran	Apixaban	Edoxaban	Rivaroxaban
Reduce absorption	–	activated charcoal until 2–4 h (up to 6 h [60])		activated charcoal until 8 h
Increase renal elimination	secure effective diuresis	sorbitol	secure effective diuresis	secure effective diuresis
Hemodialysis	possible, limited experience <sup>1</sup>	not effective	not effective	not effective

<sup>1</sup>Also risk of bleeding at puncture site [29].

whereas levels > 200 ng/ml are associated with a significant bleeding risk [52, 53].

With plasma levels between 30 and 200 ng/ml, each case needs to be assessed individually, depending on the bleeding risk [29, 52] (fig. 1).

#### *Spinal and Epidural Anesthesia in Patients Treated with NOACs*

Guidelines that tackle NOAC management in neuraxial anesthesia make different recommendations about when to stop and when to resume these drugs before and after an intervention. The French Group on Perioperative Hemostasis (GIHP) for example recommends not to perform regional anesthesia techniques as long as a NOAC concentration is still prevalent [55]. Other recommendations suggest different timing schemes of cessation and re-initiation of anticoagulant treatment [56–58], or, depending on the type of anesthesia, if discontinuation is even necessary at all [56].

No definite evidence is available on this topic. The authors of this paper made a consensus-based conclusion: Both neuraxial puncture and the removal of a catheter have a comparable bleeding risk. The NOAC-free interval before these procedures corresponds with the surgical interventions with high bleeding risk, i.e. at least 5 half-lives (table 7).

Deep nerve blocks like psoas compartment or infraclavicular blocks are considered to carry the same bleeding risk as spinal and epidural anesthesia.

#### *Re-Start of NOACs after Intervention*

Same as before when undergoing surgery, the management of anticoagulation after an intervention needs to balance the bleeding risk of the intervention and the thromboembolic risk of the patient. The drug-specific guidelines indicate re-initiation of anticoagulation as soon as sufficient hemostasis has been accomplished (table 8) [6–9].

In patients at high risk of thromboembolism, postoperative bridging with low-molecular-weight heparin or intravenous unfractionated heparin (according to insti-

tution protocol) can be considered until therapeutic anticoagulation can be re-introduced [59]; a reduced dose (e.g. rivaroxaban 1 × 10 mg/day) or mechanical prophylaxis such as intermittent pneumatic compression can also be considered [59].

### **Overdoses, Intoxications and Bleeding**

#### *Management of Overdoses and Intoxications*

Overdoses of NOACs may occur in worsening of renal or hepatic function, incidentally or with suicidal intentions. If the elimination of the drug is not significantly reduced, the relatively short half-life of NOACs is an advantage compared to VKAs. In an unclear situation it may be helpful to determine plasma levels. Countermeasures may be considered, depending on the situation (table 9).

#### *Management of Active Bleeding*

When bleeding occurs, it is important to first assess the event according to severity of blood loss and location. Once more, it would be important to know the time of last intake and type of NOAC used as well as other factors that might influence plasma concentration and hemostasis [29]. In most non-life-threatening bleeding events, the temporary discontinuation of the NOAC and supportive care are sufficient to control the problem [61]. In a study with patients using rivaroxaban, even the majority of major bleedings (as defined by the International Society on Thrombosis and Hemostasis) could be managed with local therapy or red blood cell transfusions, with only 37% requiring an intervention or surgery [62].

If the clinical situation calls for a more urgent procedure, specific or non-specific reversal agents can be considered [63].

Currently, only dabigatran can be counteracted with a direct (or specific) reversal agent, idarucizumab (approved 2015 in the US and Europe and 2016 in Switzerland). It is highly important to repeat all coagulation tests 10 min after the administration of idarucizumab, because

**Table 10.** Management of active bleeding, adapted after [31, 65]

General parameters		
Diagnostic	Patient history <ul style="list-style-type: none"><li>• Time of last NOAC intake</li><li>• Medication interactions</li><li>• Potential accumulation (e.g. renal insufficiency)</li><li>• Co-medication with platelet aggregation inhibitors</li></ul> Blood count, PT/INR, aPTT, thrombin time, fibrinogen Renal function	
	Minor bleeding	Severe bleeding
Therapeutic FXa	<ul style="list-style-type: none"><li>• Symptomatic measures</li><li>• Mechanical compression</li><li>• Interventional hemostasis</li><li>• Tranexamic acid i.v. 10–15 mg/kg, then 1–5 mg/kg/h.</li><li>• Skip the next dosage. An interruption of the anticoagulation is usually not necessary</li></ul>	<ul style="list-style-type: none"><li>• Symptomatic measures</li><li>• Mechanical compression</li><li>• Interventional hemostasis</li><li>• Activated charcoal, in case of last intake &lt; 2 h</li><li>• Tranexamic acid i.v. 10–15 mg/kg, then 1–5 mg/kg/h. CAVE: caution by hematuria</li><li>• Desmopressin 0.3 µg/kg i.v.</li><li>• PCC</li><li>• 3-factor and 4-factor preparations can be used in case of severe bleeding</li><li>• aPCC, like rFVIIa, only in case of life-threatening intractable bleeding</li><li>• Antidote andexanet alfa (if available)</li><li>• Platelet transfusion when platelet count &lt; 50 G/l If the bleeding is controlled:</li><li>• Evaluation of prophylactic anticoagulation</li><li>• Interruption/cessation of anticoagulation, depending on the bleeding complication and the indication for anticoagulation</li></ul>
	Dabigatran	<ul style="list-style-type: none"><li>• Mechanical compression</li><li>• Interventional hemostasis</li><li>• Tranexamic acid 1 g i.v.</li><li>• Skip the next dosage. An interruption of the anticoagulation is usually not necessary</li></ul>

PT = Prothrombin time; aPTT = activated partial prothromboplastin time; INR = internalized normalized ratio; i.v. = intravenous  
PCC = prothrombin complex concentrates; aPCC = activated prothrombin complex concentrates; rFVIIa = recombinant factor VIIa

PT = Prothrombin time; aPTT = activated partial prothromboplastin time; INR = internalized normalized ratio; i.v. = intravenous; PCC = prothrombin complex concentrates; aPCC = activated prothrombin complex concentrates; rFVIIa = recombinant factor VIIa.

only then other coagulation problems of the patient can be clearly diagnosed.

For FXa inhibitors the reversal agent andexanet alfa may soon be available (approved May 2018 in the US). Should a direct reversal agent not be available, the Swiss Society for Anesthesiology and Reanimation recommends the administration of tranexamic acid and potentially desmopressin to attempt a normalization of hemostasis, before using concentrates with pro-coagulant factors such as prothrombin complex concentrate (PCC) in severe bleeding [31, 64]. Activated PCC should only be considered in a patient with life-threatening, intractable bleeding [29, 63].

Once the bleeding has been stopped, thromboembolic prophylaxis needs to be restarted in all patients as soon as possible, as patients under oral anticoagulation are particularly prone to thrombosis and thromboembolic complications (table 10).

## Outlook

Currently under investigation are two more reversal agents, andexanet alfa (targeting all FXas) and PER977 (or aripazine or ciraparantag, targeting FXa inhibitors, dabigatran and heparins) [61].

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